Second-line drug therapy for osteoarthritis

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For treatment of patients with rheumatoid arthritis, drugs and biologicals are now available which are not primarily analgesics or anti-inflammatory agents but which have the capacity to prevent or slow structural damage in the rheumatoid joint (eg methotrexate, leflunomide, etanercept, infliximab). Similarly, in animal models of osteoarthritis (OA), pharmacological and biological agents have been identified whose primary action is not the reduction of joint pain or inflammation (as with first-line therapy), but which can prevent structural damage in a joint at high risk for developing OA and/or slow the progression of tissue damage in a joint in which OA is already established. Such agents, which are viewed as potential second-line therapy for OA, have been designated disease-modifying OA drugs (DMOADs)[1]. To date, none of these agents has been convincingly shown to have disease-modifying activity in humans with OA.

Disease-modifying osteoarthritis drugs

Most DMOADs decrease articular cartilage levels of matrix metalloproteinases (MMPs) (eg collagenase, gelatinase, stromelysin) which have been implicated in damage of the cartilage in OA. Some DMOADs have broad specificity against MMPs, while others have relatively high specificity against one MMP[2].

Doxycycline

Doxycycline, the DMOAD effect of which we are currently evaluating in a placebo-controlled clinical trial, initially generated interest as a possible DMOAD when it was shown to inhibit *in vitro* the 92 kDa gelatinase which degrades type XI collagen in articular cartilage, and that this inhibition could be reversed by addition of small amounts of the divalent cations, calcium or zinc[3]. These observations led to *in vivo* studies in canine cruciate-deficiency models of OA, in which doxycycline was shown to possess DMOAD activity regardless of whether it was administered prophylactically (ie promptly after the induction of joint instability)[4] or therapeutically (ie after joint damage has already been established)[5]. Evidence supporting these observations was subsequently obtained with other animal models of OA[6,7] and with chemically modified tetracyclines.

The initial impression was that doxycycline exerted its effect through chelation either of the calcium atoms which are essential for the molecular stability of MMPs or of the zinc atom which is present at the active site of these enzymes. This could not, however, explain the observation that striking reductions were observed not only in levels of the active MMPs, but also in the levels of total MMP in the cartilage after administration of doxycycline in animal models of OA[4] or to humans with the disease[8]. Further work aimed at elucidating the underlying mechanism of action has indicated that doxycycline may inhibit transcription of mRNA involved in MMP synthesis[9] and of mRNA for inducible nitric oxide synthase (iNOS)[10] – an enzyme whose action results in the generation within cartilage of nitric oxide, a powerful stimulant of the production and release of MMPs by chondrocytes[11]. Other work has shown that doxycycline may inhibit the translation of MMPs[12].

Anthraquinones

There is also interest currently in the anthraquinone, diacerhein, as a potential DMOAD. This drug has been shown to slow the development of chondropathy in a canine cruciate-deficiency model[13]. In support of these data, a placebo-controlled clinical trial of diacerhein in humans with hip OA has suggested a significant DMOAD effect in those who completed the three-year period of treatment[14].

Glucosamine

Glucosamine sulphate slows the progression of joint damage in patients with knee OA, as reflected by changes in the rate of narrowing of the joint space of the medial tibiofemoral compartment in standing knee radiographs[15,16]. However, because the patients treated with glucosamine reported a decrease in joint pain in comparison with those who received placebo, it is possible that an increase in knee extension associated with the decrease in pain may itself increase the

Key Points

Osteoarthritis is a disease of an organ (the synovial joint) and not of only a single tissue, such as articular cartilage. In osteoarthritis, all of the tissues of the joint are involved – the subchondral bone, synovium, ligaments, periarticular muscle and articular nerves – not only the cartilage

Even if a therapeutic agent is shown convincingly to slow the progression of cartilage damage in an osteoarthritic joint, it is unclear whether this 'chondroprotection' will be accompanied by improvement in clinically important outcomes, such as an increase in the time to disability or decrease in the frequency of total joint arthroplasty

Although a number of drugs have demonstrated structure-modifying effects in animal models of osteoarthritis, none has yet been shown convincingly to have this effect in humans with osteoarthritis

interbone distance on the radiograph without necessarily affecting the thickness of the articular cartilage. Furthermore, concerns have been expressed about the reproducibility of positioning of the joint when conventional standing knee radiographs are used in OA progression studies (as in the clinical trials of glucosamine), raising questions about the adequacy of sample sizes in such studies.

Side effects of matrix metalloproteinase inhibition

Although the above developments are encouraging, there is concern about potential side effects of MMP inhibition. Reports of the development of cancer in some subjects who were treated with an MMP inhibitor and of an increase in fibrosis in others treated with a different MMP inhibitor have tempered the enthusiasm of some pharmaceutical companies for DMOAD development. In addition, it is by no means clear that demonstration of a pharmacologically or biologically mediated chondroprotective effect will be accompanied by improvement in joint pain, a decrease in disability or a reduction in the need for costly total joint arthroplasty.

Evaluation of disease-modifying osteoarthritis drugs

Uncertainty also exists with regard to the outcome measures required to evaluate a DMOAD effect. While magnetic resonance imaging (MRI) has great sensitivity, it has not been validated as an outcome measure in OA clinical trials. Conventional radiography is relatively inexpensive and easily performed, but it has significant limitations because of the lack of reliability of the procedure[17]. Newer radiographic approaches aim to provide reproducible radioanatomical positioning of the joint by employing fluoroscopy[18] which, however, increases costs, may present logistic barriers (eg an elective knee radiograph competing with an emergency MRI of the head in the clinical radiology department), and results in some radiation exposure of the subject. Efforts to standardise the positioning of the knee by non-fluoroscopic methods are now receiving attention[19,20], but their reliability in clinical trials has yet to be established.

Conclusions

The great gains achieved recently in our understanding of the pathobiology and pathobiochemistry of cartilage damage in OA have led to efforts within the pharmaceutical industry and in academia to develop agents which inhibit cartilage MMPs. It remains to be seen whether any of these will prove to be clinically useful DMOADs. Even if this should prove to be the case, it is uncertain whether DMOADs will have a beneficial effect on symptoms or disability. The correlation between progression of radiographic changes of OA and progression of joint pain and disability is not strong[21].

Given the understandable interest in the development of second-line drug therapy for OA, it should be noted that current first-line therapy leaves much to be desired. The recent availability of coxibs (COX-1 sparing non-steroidal anti-inflammatory drugs (NSAIDs)) may significantly decrease the risk of a serious upper gastrointestinal adverse event (eg ulcer, haemorrhage, obstruction, perforation). However, these drugs are no more effective than non-opioid analgesics such as paracetamol or NSAIDs[22], and have similar adverse effects on renal function, fluid retention, blood pressure elevation, precipitation of congestive heart failure, etc[23]. Additionally, the magnitude of improvement in joint pain achieved today with first-line agents is only modest. Based on measurements on visual analogue scales, improvement in joint pain with the currently available agents is only 20–25%, while that with placebo may be 15%[24–27]. This may account for the observation that only about 15% of patients with OA who were started on an NSAID were still taking the same NSAID 12 months later[28]. While efforts to develop DMOADs are laudable, more effective and safer first-line drugs for OA are needed. This need should not be ignored.

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